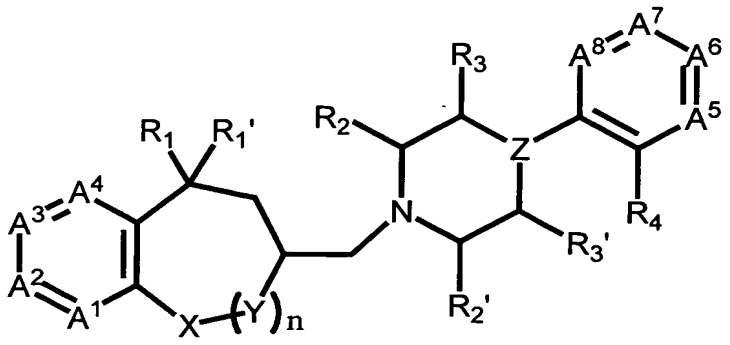
CLAIMS

1. A cycloalkanopyridine derivative of the following general formula [I], and pharmaceutically-acceptable salt thereof:



[I]

wherein;

A^1, A^2, A^3 and A^4 each independently represent -C(R_5)- or -N-,provided that at least one of A^1, A^2, A^3 and A^4 is -N-;

A^5, A^6, A^7 and A^8 each independently represent -C(R_6)- or -N-;

R_1 and R_1' each independently represent a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, a C_{1-6} alkyloxy group, a C_{1-6} alkyloxyalkyloxy group, a C_{1-6} alkyloxycarbonyl group, a C_{1-6} alkyloxycarbonylamino group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkylcarbonyloxy group, a C_{1-6} alkylcarbonylamino group, a C_{1-6} alkylsulfonyl group, a C_{1-6} alkylsulfonylamino group, a C_{1-6} alkylsulfonyl-C_{1-6} alkylamino group, a carbamoylamino group, a (C_{1-6} alkyl)carbamoylamino group, a di(C_{1-6} alkyl)carbamoylamino group, a pyrazolyl group, a triazolyl group, an oxazolyl group, or a C_{1-6} alkyl group optionally having a substituent selected from the following group [α]; or R_1 and R_1' together form an oxo group or a C_{1-3} alkyleneketal group;

R_2 represents a hydrogen atom or a C_{1-6} alkyl group optionally having a hydroxyl group, or R_2 and R_2' or R_3' together form a C_{1-3} alkylene group or an oxy-C_{1-3} alkylene group;

R_2' represents a hydrogen atom or a C_{1-6} alkyl group optionally having a hydroxyl group, or R_2' and R_2 or R_3 together form a C_{1-3} alkylene group or an oxy-C_{1-3} alkylene group;

R_3 represents a hydrogen atom, a hydroxyl group, a halogen atom, a C_{1-6} alkyloxy group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkyloxycarbonyl group, a C_{1-6} alkylsulfonyl group, a C_{1-6} alkylsulfonylamino group, a C_{1-6} alkylsulfonylalkylamino group, a cyano group, or a C_{1-6} alkyl group optionally having a substituent selected from the group [α]; or R_3 and R_3' or R_2' together form a C_{1-3} alkylene group or an oxy-C_{1-3} alkylene group;

R_3' represents a hydrogen atom, a hydroxyl group, a halogen atom, a C_{1-6} alkyloxy group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkyloxycarbonyl group, a C_{1-6} alkylsulfonyl group, a C_{1-6} alkylsulfonylamino group, a C_{1-6} alkylsulfonylaminoalkyl group, a cyano group, or a C_{1-6} alkyl group optionally having a substituent selected from the group [α]; or R_3' and R_3 or R_2 together form a C_{1-3} alkylene group or an oxy-C_{1-3} alkylene group;

R_4 represents a hydrogen atom, a halogen atom, a C_{1-6} alkyl group optionally having a hydroxyl group, a halogeno-C_{1-6} alkyl group, a C_{1-6} alkyloxy-C_{1-6} alkyl group, a C_{1-6} alkylcarbonyl group, a cyano group, a formyl group, a C_{1-6} alkyloxycarbonyl group, a C_{1-6} alkylcarbonylamino group, a C_{1-6} alkylcarbonyl-C_{1-6} alkylamino group or a C_{1-6} alkylsulfonyl group; or when Z is -$C(R_7)$-, then R_4 and R_7 together form -$C(R_8)(R_8')$-O-, -$C(R_8)(R_8')$-CO-, -$C(R_8)(R_8')$-$C(R_8)(R_8')$-, -O-CO-, -CO-O-, -CO-$C(R_8)(R_8')$-, -O-$C(R_8)(R_8')$-, -$CH(R_8)$-$N(R_9)$- or -$N(R_9)$-$CH(R_8)$-;

R_5 represents a hydrogen atom, a hydroxyl group, a fluorine atom, a chlorine atom, a C_{1-6} alkyl group, a C_{1-6} alkylamino group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkylcarbonylamino group, a C_{1-6} alkylcarbonyl-(C_{1-6})alkylamino group, or a cyano group;

R_6 represents a hydrogen atom, a halogen atom, a C_{1-6} alkyl group optionally having a hydroxyl group, a halogeno-C_{1-6} alkyl group, a C_{1-6} alkyloxy-C_{1-6} alkyl group, a C_{1-6} alkylcarbonyl group, a cyano group, a formyl group, a C_{1-6} alkyloxycarbonyl group, a C_{1-6} alkylcarbonylamino group, a C_{1-6} alkylcarbonyl-C_{1-6} alkylamino group, or a C_{1-6} alkylsulfonyl group;

R_7 represents a hydrogen atom, a halogen atom, a cyano group, a C_{1-6} alkyl group, a C_{1-6} alkyloxy group; or R_7 and R_4 together form -$C(R_8)(R_8')$-O-, -$C(R_8)(R_8')$-CO-, -$C(R_8)(R_8')$-$C(R_8)(R_8')$-, -O-CO-, -CO-O-, -CO-$C(R_8)(R_8')$-, -O-$C(R_8)(R_8')$-, -$CH(R_8)$-$N(R_9)$- or -$CH(R_8)$-$N(R_9)$-;

R_8 and R_8' each independently represent a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group optionally having a hydroxyl group, or a C_{1-6} alkylsulfonyl group;

R_9 represents a hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkylsulfonyl group, a C_{1-6} alkyloxycarbonyl group, or a formyl group;

Ra represents a hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkyloxycarbonyl group, a carbamoyl group, a (C_{1-6} alkyl)carbamoyl group, a di(C_{1-6} alkyl)carbamoyl group, a C_{1-6} alkylsulfonyl group, a pyrazolyl group, a triazolyl group, or an oxazolyl group;

X represents -CH_2-, -CH(OH)-, -N(Ra)-, -O-, -S- or -SO_2-;

Y represents -CH_2- or -N(Ra)-;

Z represents -$C(R_7)$- or -N-;

n indicates an integer of 0 or 1;

Group α: a halogen atom, a hydroxyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkylcarbonyloxy group, a C_{1-6} alkylcarbonylamino group, a C_{1-6} alkylcarbonyl-C_{1-6} alkylamino group, a C_{1-6} alkyloxy group, a C_{1-6} alkyloxycarbonyl group, a C_{1-6} alkyloxycarbonylamino group, a C_{1-6} alkyloxycarbonyl-C_{1-6} alkylamino group, a C_{1-6} alkylamino group, a di-C_{1-6} alkylamino group, a sulfamoyl group, a C_{1-6} alkylsulfamoyl group, a di-C_{1-6} alkylsulfamoyl group, a sulfamoylamino group, a C_{1-6} alkylsulfamoylamino group, a di-C_{1-6} alkylsulfamoylamino group, a C_{1-6} alkylsulfamoyl-C_{1-6} alkylamino group, a di-C_{1-6} alkylsulfamoyl-C_{1-6} alkylamino group, a sulfamoyloxy group, a C_{1-6} alkylsulfamoyloxy group, a di- C_{1-6} alkylsulfamoyloxy group, a carbamoyl group, a C_{1-6} alkylcarbamoyl group, a di-C_{1-6} alkylcarbamoyl group, a carbamoylamino group, a C_{1-6} alkylcarbamoylamino group, a di-C_{1-6} alkylcarbamoylamino group, a C_{1-6} alkylcarbamoyl-C_{1-6} alkylamino group, a di-C_{1-6} alkylcarbamoyl-C_{1-6} alkylamino group, a carbamoyloxy

group, a C_{1-6} alkylcarbamoyloxy group, a di-C_{1-6} alkylcarbamoyloxy group, a C_{1-6} alkylsulfonyl group, a C_{1-6} alkylsulfonylamino group, and a C_{1-6} alkylsulfonyloxy group.

2. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, wherein A^4 is -N-, and A^1, A^2 and A^3 are all -C(R_5)-.

3. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1 or 2, wherein A^5, A^6, A^7 and A^8 are all -C(R_6)-.

4. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1 or 2, wherein A^7 is -N-, and A^5, A^6 and A^8 are all -C(R_6)-.

5. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 3 or 4, wherein R_6 is selected from a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, an ethyl group, an isopropyl group, a trifluoromethyl group, a methylcarbonyl group, a methoxymethyl group, a formyl group and a cyano group.

6. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, wherein R_1 and R_1' are selected from a hydrogen atom, a hydroxyl group, a methyl group, a methoxy group, a methylsulfonylamino group and a methylcarbonylamino group.

7. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, wherein R_1 and R_1' together form an oxo group or an ethylene-ketal group.

8. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, wherein R_2 and R_2' are both hydrogen atoms.

9. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, wherein R_2 and R_2' together form -CH_2CH_2-.

10. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, wherein R_3 and R_3' are selected from a hydrogen atom, a hydroxyl group, a fluorine atom, a methoxy group, a methyl group, a hydroxymethyl group, a fluoromethyl group, a methanesulfonylaminomethyl group, a methanesulfonylmethylaminomethyl group, a methoxycarbonylaminomethyl group and a dimethylsulfamoylaminomethyl group.

11. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, wherein R_4 is selected from a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, an ethyl group, a cyano group, a formyl group and a trifluoromethyl group.

12. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, wherein R_4 and R_7 together form -CH_2-O-, -CH(CH_3)-O-, -C(CH_3)$_2$-O- or -N(CH_3)-CH_2-.

13. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, wherein Z is -C(R_7)-, and R_7 is selected from a hydrogen atom, a fluorine atom and a methyl group.

14. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, wherein X is -CH_2-, -O- or -N(CH_3)-.

15. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, wherein n = 0.

16. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, wherein n = 1 and Y is $-CH_2-$.

17. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, selected from the following:

(7R,9S)-7-(spiro[8-aza-biycyclo[3.2.1]octa-3,1'(3'H)-isobenzofuran]-8-ylmethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol;

(6R,8S)-6-(spiro[isobenzofuran-1-(3H),4'-piperidin]-1'-ylmethyl)-5,6,7,8-tetrahydroquinolin-8-ol);

(7R,9S)-7-[(3R*,4R*)-3-hydroxy-4-o-tolyl-piperidin-1-ylmethyl]-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol;

(7R,9S)-7-[(3R*,4R*)-(4-fluoro-o-tolyl)-3-hydroxypiperidin-1-ylmethyl]-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol;

(7R,9S)-7-(6'-aza-5'-fluoro-spiro[8-aza-bicyclo[3.2.1]-octa-3,1'(3'H)-isobenzofuran]-8-ylmethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol;

(6R,8S)-6-(3,3-dimethyl-spiro[isobenzofuran-1(3H),4'-piperidin-1'-ylmethyl)-5,6,7,8-tetrahydro-quinolin-8-ol;

(7R,9S)-7-(1-methylspiro-[2,3-dihydro-1H-indol-3,4'-piperidin]-1'-ylmethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol;

(6R,8S)-6-[4-(2-chlorophenyl)-4-fluoropiperidin-1-ylmethyl]-5,6,7,8-tetrahydroquinolin-8-ol;

(7R,9S)-7-[(3R*,4R*)-4-(2-chlorophenyl)-3-hydroxypiperidin-1-ylmethyl]-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol;

(7R,9S)-7-[(3R,4R)-4-(2-chloro-4-fluorophenyl)-3-hydroxypiperidin-1-ylmethyl]-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol;

(6R,8S)-6-[(3R,4R)-4-(2-chloro-4-fluorophenyl)-3-hydroxypiperidin-1-ylmethyl]-5,6,7,8-tetrahydroquinolin-8-ol;

(7R,9S)-7-[(3R*,4S*)-3-hydroxymethyl-4-phenyl-piperidin-1-ylmethyl]-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol;

(7R,9S)-7-[(3R*,4S*)-3-methyl-4-phenylpiperidin-1-ylmethyl]-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol;

N-{(7R,9S)-7-[(3R,4R)-4-(2-chloro-4-fluorophenyl)-3-hydroxypiperidin-1-ylmethyl]-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl}methanesulfonamide;

(6R,8S)-6-[(5'-fluoro-3',3'-dimethyl-3'H-6'-azaspiro[8-azabicyclo[3.2.1]octane-3,1'-isobenzofuran]-8-yl)methyl]-5,6,7,8-tetrahydroquinolin-8-ol; and

(6R,8S)-6-[(1S*,2R*,3R*)-3-(2-chloro-4-fluorophenyl)-2-hydroxy-8-azabicyclo[3.2.1]octan-8-ylmethyl]-5,6,7,8-tetrahydroquinolin-8-ol.

18. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, which is (7R,9S)-7-[(3R*,4R*)-3-hydroxy-4-o-tolyl-piperidin-1-ylmethyl]-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol.

19. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, which is (7R,9S)-7-[(3R*,4R*)-(4-fluoro-o-tolyl)-3-hydroxypiperidin-1-ylmethyl]-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol.

20. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, which is (7R,9S)-7-(6'-aza-5'-fluoro-spiro[8-aza-bicyclo[3.2.1]-octa-3,1'(3'H)-isobenzofuran]-8-ylmethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol.

21. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, which is (7R,9S)-7-[(3R*,4R*)-4-(2-chlorophenyl)-3-hydroxypiperidin-1-ylmethyl]-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol.

22. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, which is (6R,8S)-6-[(3R,4R)-4-(2-chloro-4-fluorophenyl)-3-hydroxypiperidin-1-ylmethyl]-5,6,7,8-tetrahydroquinolin-8-ol.

23. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, which is N-{(7R,9S)-7-[(3R,4R)-4-(2-chloro-4-fluorophenyl)-3-hydroxypiperidin-1-ylmethyl]-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl}methanesulfonamide.

24. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, which is (6R,8S)-6-[(5'-fluoro-3',3'-dimethyl-3'H-6'-azaspiro[8-azabicyclo[3.2.1]octane-3,1'-isobenzofuran]-8-yl)methyl]-5,6,7,8-tetrahydroquinolin-8-ol.

25. The compound or pharmaceutically-acceptable salt thereof as claimed in claim 1, which is (6R,8S)-6-[(1S*,2R*,3R*)-3-(2-chloro-4-fluorophenyl)-2-hydroxy-8-azabicyclo[3.2.1]octan-8-ylmethyl]-5,6,7,8-tetrahydroquinolin-8-ol.

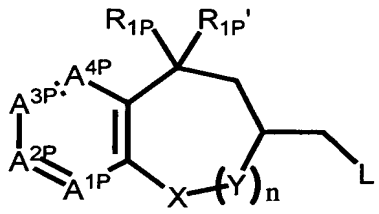
26. A nociceptin receptor antagonist containing a compound of formula [I] as the active ingredient thereof.

27. A pharmaceutical composition comprising a compound of formula [I] and a pharmaceutically-acceptable additive.

28. An analgesic; a reliever against tolerance to a narcotic analgesic such as morphine; a reliever against dependence on or addiction to a narcotic analgesic such as morphine; an analgesic enhancer; an antiobesitic or appetite suppressor; a treating or prophylactic agent for cognitive impairment and dementia/amnesia in aging, cerebrovascular diseases and Alzheimer's disease; an agent for treating developmental cognitive abnormality such as attention deficit hyperactivity disorder and learning disability; a remedy for schizophrenia; an agent for treating neurodegenerative diseases such as Parkinsonism and chorea; an anti-depressant or treating agent for affective disorder; a treating or prophylactic agent for diabetes insipidus; a treating or prophylactic agent for polyuria; or a remedy for hypotension; which contains a compound of formula [I] as the active ingredient thereof.

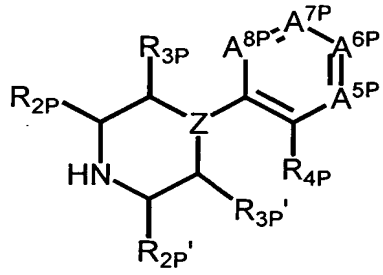
29. A method for producing a compound of formula [I], which includes;

1) a sep of condensing a compound of a general formula [II]:



[II]

[wherein L represents a leaving group; R_{1P} represents R_1 optionally having a protective group; R_{1P}' represents R_1' optionally having a protective group; A^{1P} represents A^1 optionally having a protective group; A^{2P} represents A^2 optionally having a protective group; A^{3P} represents A^3 optionally having a protective group; A^{4P} represents A^4 optionally having a protective group; X, Y and n have the same meanings as in claim 1], with a compound of a general formula [III]:



[III]

[wherein R_{2P} represents R_2 optionally having a protective group; R_{2P}' represents R_2' optionally having a protective group; R_{3P} represents R_3 optionally having a protective group; R_{3P}' represents R_3' optionally having a protective group; R_{4P} represents R_4 optionally having a protective group; A^{5P} represents A^5 optionally having a protective group; A^{6P} represents A^6 optionally having a protective group; A^{7P} represents A^7 optionally having a protective group; A^{8P} represents A^8 optionally having a protective group; Z has the same meaning as in claim 1];

2) when the compound obtained in the previous step has a protective group, a step of removing the protective group.